REMARKS

Claims 1-11, 13-19 and 32-49 are pending in the present application. Claims 20-31 were previously cancelled. Claims 19 and 40-45 were previously withdrawn from consideration. By virtue of this response, claims 9-11, 13, 16-18, and 34-35 have been cancelled, claims 1, 14-15, 32-33, 37-39, and 46-49 have been amended and new claims 50-55 have been added. Accordingly, claims 1-8, 14-15, 32-33, 36-39, and 46-55 are currently under consideration.

Amendments to the Claims

Claim 1 has been amended. Support for the amendment of claim 1 may be found, for example, on page 4, line 33, page 5, lines 22-29, page 10, line 27 – page 11, line 7, page 21, lines 3-6, page 27, lines 16-36, and page 45, lines 29-31. "S2C6" (SGN-14) is an anti-CD40 antibody disclosed in International Publication No. WO 00/75348 A1 [Siegall] and in U.S. Patent No. 6,843,989 B1 [Siegall], column 8, lines 45-67; column 9, lines 1-7, and column 34, lines 10-19.

The Siegall patent discloses the S2C6 antibody is a monoclonal antibody secreted from hybridoma S2C6, which has ATCC accession number PTA-110. The Siegall International Publication (application) is CIP of U.S. Appl. No. 09/328,296 which is a priority application for the U.S. Siegall patent. Both the Siegall International Publication and the Siegall U.S. patent are incorporated by reference in the instant application (*see*, for example, page 44, lines 23-25). Thus, the specification has support for the ATCC accession No. PTA-110.

Claims 14, 15, 32-33, and 46-49 have been amended to change dependency, address clerical mistakes, and/or further clarify the claimed invention.

Support for new claim 50 may be found, for example, on page 10, line 27 – page 11, line 2. Support for new claim 51 may be found, for example, on page 9, line 29 – page 10, line 3 and page 11, line 30 – page 12, line 11. Support for new claim 52 may be found, for example, on page 27, lines 16-23. Support for new claims 53-54 may be found, for example, on page 27, lines 26-31.

Support for the amendment of claim 39 and new claim 55 may be found, for example, on page 11, lines 3-7 and page 21, lines 15-17. The anti-CD20 antibody is identified in the instant specification (*see*, for example, page 17, lines 3-7; page 21, lines 15-17) as rituximab, which is identified as the "C2B8" antibody in U.S. Patent No. 5,736,137 [Anderson] (column 21, beginning at line 19).

The Anderson patent discloses the nucleotide sequence encoding the "C2B8" antibody (rituximab) is in TCAE 8 (a transformed E. coli for purposes of deposit) having ATCC accession number 69119 (anti-CD20 in TCAE 8) (column 32, lines 13-27). The Anderson patent is incorporated by reference in the instant application (*see*, for example, page 44, lines 23-25). Thus, the instant specification has support for the monoclonal antibody produced by the transfectoma having ATCC accession number 69119.

No new matter is added.

With respect to all amendments to claims, Applicants have not dedicated or abandoned any unclaimed subject matter and, moreover, have not acquiesced to any rejections and/or objections made by the Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation, continuation-in-part, and/or divisional applications.

Substance of Interview Summary

An interview with Examiner Gambel was held by telephone on March 12, 2008. In addition to Examiner Gambel and Jie Zhou (the undersigned), Stephanie Yonker participated in the interview. Applicants and their representatives would again like to thank Examiner Gambel for the courtesy of the telephonic interview. The subject of the telephonic interview was the § 102(e) and § 103(a) rejections related to the Hanna et al. reference.

Withdrawn Claims

The Examiner states that claims 19 and 40-45 are withdrawn from consideration as being directed to a non-elected invention or species.

Applicants respectfully note that claims 19 and 40-45 have been withdrawn without traverse.

Objections to the Claims

(A) The Examiner objects to claims 37-38, stating that the ATCC Accession No. 69119 refers to the S2C6 antibody and not to the SGN-114, as currently recited.

Applicant respectfully notes that claims 37 and 38 have been amended to recite "S2C6". Applicant further notes that the ATCC Accession No. recited in claims 37-38 is PAT-110, not 69119. Accordingly, Applicant respectfully requests that this objection be withdrawn.

(B) The Examiner objects to claim 39, stating "rutuximab" should be "rituximab".

Applicant respectfully notes that claim 39 has been amended to change "rutuximab" to "rituximab". Accordingly, Applicant respectfully requests that this objection be withdrawn.

(C) The Examiner objects to claims 47 and 49, stating that "F(ab')2" should be "$F(ab')_2$".

Applicant respectfully notes that claims 47 and 49 have been amended to change "F(ab')2" to "$F(ab')_2$". Accordingly, Applicant respectfully requests that this objection be withdrawn.

Claim Rejections under 35 U.S.C. § 102(e)

Claims 1-11, 13-18, 32-33 and newly submitted claims 34-35 and 46-49 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Hanna et al. (US 20001/0018041 A1) and in further evidence of Armitage et al. (U.S. Patent No. 5,674,492 cited in paragraphs [0013] and [0104] of Hanna et al.), wherein said teachings of agonistic anti-CD40 are acknowledged by page 2, paragraph 1 of the instant specification and paragraphs [0005] and [0036] of Fanslow et al., US 2005/0129689 A1) essentially for the reasons of record.

Applicant respectfully traverses this rejection.

Applicant respectfully notes that claims have been amended to recite a method for treating a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal by administering a CD20 specific binding agent which is an anti-CD20 antibody, and a CD40 specific binding agent that arrests the growth of or causes deletion of cells expressing CD40 and stimulates CD40, which CD40 specific binding agent is a chimeric antibody or a humanized antibody derived from S2C6 (ATCC Accession No. PTA-110); wherein the CD20 specific binding agent and the Cd40 specific binding agent in combination inhibits the neoplastic disease or disorder in the mammal. *See* claim 1 as amended.

Applicant respectfully submits that the references cited by the Examiner do not teach or suggest to use of a chimeric or a humanized antibody derived from antibody S2C6 in combination with an anti-CD20 antibody for treatment as recited in the claims. The Examiner has acknowledged that the references cited do not teach the CD40 specific antibody S2C6 per se. *See* Office Action, page 7, first paragraph.

The Examiner further states that the inhibitory CD40-specific antibodies taught by the prior art would have the same CD40 binding characteristics under the broadest reasonable interpretation of CD40-binding antibodies in the absence of limitations to the contrary. Applicant respectfully disagrees with the Examiner, and submits that the anti-CD40 antibodies, specifically M2 and M3 disclosed in Hanna et al., have characteristics different from antibody S2C6. As noted in the specification of the present application, antibody M2 and antibody M3 were selected based upon their ability to inhibit the binding of CD40 to cells expressing CD40L, and CD40 stimulation by M2 and M3 inhibits growth of several B-cell lymphomas and induces regression of established tumors in vivo. *See* Specification at page 19, lines 20-27. The specification states that antibody S2C6, in addition to delivering a stimulatory signal, enhances the interaction between CD40 and CD40L. *See* Specification at page 19, lines 29-33. In view of the difference in characteristics between antibodies

M2 and M3 and antibody S2C6, one skilled in the art would not recognize that the disclosure of Hanna et al. includes use of CD40 specific antibodies having characteristics of antibody S2C6.

In view of the above, Applicant respectfully submits that claims as amended are not anticipated by Hanna et al. and in further evidence by Armitage et al. and Fanslow et al. Applicant respectfully requests the rejection under 35 U.S.C. §102(e) be withdrawn.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-11, 13-18, 32-39 and 46-49 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Hanna et al. (US 2001/0018041 A1) in view of Siegel et al. (U.S. Patent No. 6,843,989) and Grille-Lopez (U.S. Patent No. 6,455,043), and further in view of Armitage et al. (U.S. Patent No. 5,674,492 cited in paragraphs [0013] and [0104] of Hanna et al.) and Benoit et al. (Immunopharmacology 35: 129-139, 1996), and in further evidence of the referenced teachings of agonistic anti-CD40 as acknowledged by page 2, paragraph 1 of the instant specification and paragraphs [0005] and [0036] of Fanslow et al., US 2005/0129689 A1) essentially for the reasons of record.

Applicant respectfully traverses this rejection. Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness.

As noted above, claims of the present application have been amended to recite that the CD40 specific binding agent is a chimeric antibody or a humanized antibody derived from antibody S2C6. Antibody S2C6 has characteristics different from antibodies M2 and M3 recited in Hanna et al. Applicant respectfully submits that references cited by the Examiner do not provide the motivation to combine teachings in these references.

Although Hanna et al. state that the invention further contemplates combining anti-CD40L antibodies with anti-CD20 antibodies and/or anti-CD40 antibodies, this reference does not teach or suggest use of antibodies with characteristics of S2C6. *See* paragraph [0104] of Hanna et al. In

addition, Example 3 of Hanna et al. showed that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody RITUXAN®. *See* Table 1. The data in this Example indicates that activation of the CD40L-CD40 pathway by soluble CD40L (sCD40L) generated resistance of RITUXAN® induced apoptosis in DHL-4 lymphoma cells. In view of the data, one skilled in the art would be not be motivated to use an anti-CD40 antibody (such as antibody S2C6) that stimulates CD40 pathway in combination with an anti-CD20 antibody for treating a neoplastic disease or disorder. Therefore, data in Hanna et al. teaches away from use of an agent that stimulates CD40 in combination with an anti-CD20 antibody for treating a neoplastic disease or disorder.

Benoit et al. do not provide further motivation to combine a chimeric antibody or a humanized antibody derived from S2C6 with an anti-CD20 antibody in the treatment of a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal. Benoit et al. discloses increased inhibition of proliferation of human B cell lymphomas following ligation of CD40 and CD20. The experiment described in this reference is based on use of anti-CD40 antibody produced by hybridoma G28.5. Benoit et al. do not disclose any other characteristics of this antibody besides it binds to CD40 and inhibits growth of certain B lymphoma cells. As indicated in Siegall et al., different anti-CD40 antibodies have different characteristics, such as on promoting CD40/CD40L interactions. *See* WO 00/75347, pages 52 to 56, sections 7.1.4, 7.1.5, 7.2.1, and 7.2.2. For example, data in Siegall et al. showed antibody S2C6 enhanced CD40/CD40L interaction in *in vitro* studies; in contrast, antibody G28-5 and antibody M3 inhibited the interaction between CD40 and CD40L. *See* WO 00/75347, page 54, line 1 to page 55, line 16. Accordingly, one skilled in the art would not view that the teachings in Benoit et al. could be applied to antibody S2C6.

Furthermore, none of Siegall et al., Grillo-Lopez, Armitage et al., and Fanslow et al. teach or provides the motivation to use an anti-CD20 antibody with a chimeric antibody or a humanized antibody derived from antibody S2C6 for treating a neoplastic disease or disorder as claimed.

In view of the above, one skilled in the art would not be motivated to administering an anti-CD20 antibody with a chimeric antibody or a humanized antibody derived from antibody S2C6 for treating a neoplastic disease or disorder as claimed.

In addition, Applicant respectfully submits that there is no reasonable expectation of success. As discussed above, data in Hanna et al. indicates that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody, RITUXAN®. In view of this teaching, one skilled in the art would not expect an anti-CD40 antibody that stimulates CD40 and enhances the interaction between CD40 and CD40L (such as S2C6) in combination with an anti-CD20 antibody would have a better effect in treating B-lymphoma as compared to use of each antibody alone. Benoit et al. only disclose use of a specific antibody G28.5 under crosslinking conditions, and Siegall et al. showed antibody G28-5 and antibody M3 inhibited the interaction between CD40 and CD40L, in contrast to the antibody S2C6 which enhanced CD40/CD40L interaction in in vitro studies. In view of the teachings in these references, one skilled in the art would not reasonably expect that an anti-CD40 antibody having characteristics of S2C6 in combination with an anti-CD20 antibody would have more than a cumulative effect in treating a neoplastic disorder or disease.

In addition, Applicant respectfully submits that specification shows that the anti-CD20 antibody used in combination with anti-CD40 antibody S2C6 have more than cumulative effect in antitumor activity. Example I of the present application is based on the experiments using anti-CD40 antibody S2C6 and anti-CD20 antibody RITUXAN®. The data in Example I shows that "[s]urvival was extended in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody compared with control animals and animals receiving anti-CD40 antibody or anti-CD20 antibody alone." *See* Specification at page 46, lines 22 -25. This result was not merely a cumulative effect based upon the use of the anti-CD40 antibody and the anti-CD20 antibody. As shown in Figure 4, three out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD40 antibody while five out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD20 antibody.

In contrast, ten out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the combination of the anti-CD20 antibody and the anti-CD40 antibody. *See* Figure 4. Further, the "[t]umor volume in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody was significantly reduced compared to control animals and animals receiving anti-C40 antibody or anti-CD20 antibody alone." *See* Specification at page 46, lines 29-33. As shown in Figure 5, one out of ten mice treated with the anti-CD40 antibody alone were tumor free (Ramos lymphoma) while ten out of ten mice treated with the combination of the anti-CD40 antibody and the anti-CD20 antibody were tumor free (Ramos lymphoma). In view of the references cited by the Examiner, this non-cumulative effect shown in Example I was surprising and unexpected.

In view of the above, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness, and claims as amended are not obvious over the references cited by the Examiner. Applicant respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 146392002400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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